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| 09/944,413      | 08/30/2001  | Kevin P. Baker       | P2548PIC3           | 2333             |

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BRINKS HOFER GILSON & LIONE  
P.O. BOX 10395  
CHICAGO, IL 60610

EXAMINER

SPECTOR, LORRAINE

| ART UNIT | PAPER NUMBER |
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1647

DATE MAILED: 01/21/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

|                              |                 |                |  |
|------------------------------|-----------------|----------------|--|
| <b>Office Action Summary</b> | Application No. | Applicant(s)   |  |
|                              | Examiner        | Group Art Unit |  |

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

**P r i d f r Response**

A SHORTENED STATUTORY PERIOD FOR RESPONSE IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a response be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for response specified above is less than thirty (30) days, a response within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for response is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to respond within the set or extended period for response will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

**Status**

- ☐ Responsive to communication(s) filed on \_\_\_\_\_.
- ☐ This action is **FINAL**.
- ☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

**Dispositi n of Claims**

- ☒ Claim(s) 22-34 is/are pending in the application.
- Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- ☒ Claim(s) 22-34 is/are rejected.
- ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- ☐ Claim(s) \_\_\_\_\_ are subject to restriction or election requirement.

**Applicati n Papers**

- ☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- ☐ The proposed drawing correction, filed on \_\_\_\_\_ is ☐ approved ☐ disapproved.
- ☐ The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.
- ☐ The specification is objected to by the Examiner.
- ☒ The oath or declaration is objected to by the Examiner.

**Pri rity under 35 U.S.C. § 119 (a)-(d)**

- ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
  - ☐ All ☐ Some\* ☐ None of the CERTIFIED copies of the priority documents have been received.
  - ☐ received in Application No. (Series Code/Serial Number) \_\_\_\_\_.
  - ☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\*Certified copies not received: \_\_\_\_\_

**Attachment(s)**

- ☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 7
- ☒ Notice of References Cited, PTO-892
- ☐ Notice of Draftsperson's Patent Drawing Review, PTO-948
- ☐ Interview Summary, PTO-413
- ☐ Notice of Informal Patent Application, PTO-152
- ☐ Other \_\_\_\_\_

**Office Acti n Summary**

**Part III: Detailed Office Action**

Claims 22-34 are pending and under consideration.

The pending claims are directed to PRO243, SEQ ID NO: 7, which is encoded by SEQ ID NO: 6, DNA 35917-1207, deposited as ATCC 209508.

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**Priority determination:**

According to the priority statement of 8/26/02, it appears that the claimed subject matter defined in the instant application is supported by the parent application serial no. PCT/US99/28301, filed 12/1/99. Based on the information given by applicant and an inspection of the patent applications, the examiner has concluded that the subject matter defined in this application is supported by the disclosure in application serial no. PCT/US99/28301, filed 12/1/99 but is not supported by any of the others because the previous disclosures do not present any enabled utility for the claimed protein. Specifically, PCT/US98/25108 does not identify PRO243 as human chordin, and does not enable the use of PRO243 for induction of fetal hemoglobin synthesis. Accordingly, the subject matter defined in claims 22-34 has an effective filing date of 12/1/99.

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Should the applicant disagree with the examiner's factual determination above, it is incumbent upon the applicant to provide the serial number and specific page number(s) of any parent application filed prior to 12/1/99 which specifically supports the particular claim limitation for each and every claim limitation in all the pending claims which applicant considers to have been in possession of and fully enabled for prior to 12/1/99.

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**Formal Matters:**

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

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The oath or declaration is defective because:

It was not executed in accordance with either 37 CFR 1.66 or 1.68. Specifically, inventor

Eaton did not provide a date of execution.

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

5

The deposit of biological organisms is considered by the Examiner to be necessary for enablement of the current invention (see MPEP Chapter 2400 and 37 C.F.R. §§1.801-1.809). Examiner acknowledges the deposit of organisms under accession number ATCC 209508 under terms of the Budapest Treaty on International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure in compliance with this requirement (see specification, page 147-148).

10

The information disclosure statement, paper number 7, has been considered. The BLAST results demonstrate that applicants are aware of proteins with identical sequences to the one claimed herein. However, as the BLAST results do not give sufficient identifying information, the Examiner cannot determine if said sequences constitute prior art.

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**Objections and Rejections under 35 U.S.C. §112:**

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

20

Claims 22-27, 30, 31, and 33-34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

25

The claims are drawn to polypeptides having at least 80%, 85%, 90%, 95% or 99% sequence identity with a particular disclosed sequence. The claims do not require that the polypeptide possess

any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of polypeptides that is defined only by sequence identity. Further, and with specific respect to claims 27 and 30-31, the claims require the 'extracellular domain' of the protein, for which there is no description in the specification.

5           To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form  
10 of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

*Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with  
15 reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure  
20 of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18  
25 USPQ2d 1016.

          One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack

of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO:7, with or without the signal sequence, but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 22-27, 30, 31, 33 and 34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the protein of SEQ ID NO: 7, with or without the signal sequence, or fragments thereof with either human chordin activity or fetal hemoglobin-inducing activity, does not reasonably provide enablement for fragments or variants that are not required to have such activity, or with claims to the ‘extracellular domain’ of the protein, regardless of activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is “undue” include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The specification discloses that PRO243 has homology to chordin (p.2), and gives expression patterns (page 97). At page 140, it is stated that PRO243 is “positive” in a rod photoreceptor cell survival assay. However, the details of the assay are minimal, for example omitting any information as to the amount of protein used or effect achieved, including the nature of any controls, such that the mere disclosure that PRO 243 is positive in the assay is insufficient to enable a person of ordinary skill in the art to use the protein for the asserted “therapeutic treatment of retinal disorders or injuries.” While disclosure that PRO243 was positive in the assay would lead the person of

ordinary skill in the art to experiment further to characterize the activity of the protein and try to determine how to use it to treat such disorders or injuries, such experimentation is part of the inventive process. A patent is granted for a completed invention, not the general suggestion of an idea and how that idea might be developed into the claimed invention. In the decision of

5 *Genentec, Inc. v. Novo Nordisk*, 42 USPQ 2d 100,(CAFC 1997), the court held that:

“[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable” and that “[t]ossing out the mere germ of an idea does not constitute enabling disclosure”. The court further stated that “when there is no disclosure of any specific starting material or of any of the conditions under  
10 which a process is to be carried out, undue experimentation is required; there is a failure to meet the enablement requirements that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art”, “[i]t is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement”.

15 The instant specification is not enabling because one cannot, following the guidance presented therein, practice the suggested methods without first making a substantial inventive contribution.

At page 146, the specification discloses that expression of PRO243 is “consistent with Cornelia de Lange syndrome.” However, such does not confer an enabled use on the claimed  
20 protein. The standard in the art is not that expression be “consistent” with a disease or syndrome; a positive association must be demonstrated. Further, the prior art does not support an association between the expression of chordin and Cornelia de Lange Syndrome (CDLS). M. Smith et al., *Human Genetics* 105:104-111, 7/8/99, teach that chordin (CHRD) is *not* likely to contribute to CDLS; see page 109, first paragraph of second column. Further, even *if* the protein was shown to  
25 be *involved* in CDLS, the specification fails to disclose how to use the claimed protein in view of such knowledge. Accordingly, no enablement is associated with the purported association to CDLS.

Therefore, the two enabled uses for the claimed protein are (a) as a dorso-ventral patterning protein, i.e. human chordin (page 147), and for the induction of fetal hemoglobin expression, as at page 142 of the specification.

30 The claims are drawn to a polypeptide having at least 80% amino acid sequence identity to the polypeptide of SEQ ID NO:7 or to portions thereof. There is no functional limitation in the

claims. Applicants have taught the polypeptide consisting SEQ ID NO:7, as well as the putative signal sequence (approximately amino acids 1-24 of SEQ ID NO:7, Figure 4).

The claims encompass an unreasonable number of inoperative polypeptides, which the skilled artisan would not know how to use. Since PRO243 it is a secreted protein, it would be expected that the mature form would be sufficient for function in the absence of the secretory signal. As opposed to the claims, what is disclosed about PRO243 is narrow: a single polypeptide with two disclosed functions and no other obvious specific functions. The prior art does teach human chordin (see art rejections below), however, the skill in the chordin art is not high because there is little information of changes that may be made to chordin that do not affect activity, and the specification provides only general, and not specific guidance to such.

There are no working examples of polypeptides less than 100% identical to the polypeptide SEQ ID:7 or the mature form thereof. The skilled artisan would not know how to use non-identical polypeptides on the basis of teachings in the prior art or specification unless they possessed the chordin or hemoglobin-inducing functions disclosed in the instant specification. The specification does not provide guidance for using polypeptides related to (*i.e.*, 80%-99% identity) but not identical to at least amino acids 25-954 of SEQ ID NO:7 which do not have the specific disclosed activities shown for PRO243. The claims are broad because they do not require the claimed polypeptide to be identical to the disclosed sequence and because the claims have no functional limitation.

For these reasons, which include the complexity and unpredictability of the nature of the invention and art in terms of the diversity of chemokines and lack of knowledge about function(s) of encompassed polypeptides structurally related to SEQ ID NO:7, the one limited working example of PRO243 polypeptide and its two functions, the lack of direction or guidance for using polypeptides that are not identical to SEQ ID NO:7, and the breadth of the claims for structure without function, it would require undue experimentation to use the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5           Claims 22-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10           The protein identified as PRO243 is not disclosed as being expressed on a cell surface, for example see page 79 of the specification. Accordingly, the limitation that the claimed protein comprises an "extracellular domain" (for example see claim 22 part (c)) is indefinite, as the art does not recognize soluble proteins as having such domains. Further, if the protein had an extracellular domain, the recitation of "the extracellular domain"..."lacking its associated signal peptide" (claim 22, part (d), for example) is indefinite as a signal sequence is not generally considered to be part of an extracellular domain, as signal sequences are cleaved from said domains in the process of  
15           secretion from the cell.

**Rejections Over Prior Art:**

20           The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

25           (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 22-26, and 33 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by U.S. Patent Number 5,846,770 (LaVallie et al).

La Vallie et al. disclose human chordin, see SEQ ID NO: 2. SEQ ID NO: 2 of LaVallie et al. differs from SEQ ID NO: 7 of the instant application only at a single residue, residue 70. Fusion proteins are also disclosed, see abstract for example.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 27-29 and 32 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over LaVallie et al., U.S. Patent Number 5,846,770.

As discussed above, La Vallie et al. disclose human chordin, see SEQ ID NO: 2. SEQ ID NO: 2 of LaVallie et al. differs from SEQ ID NO: 7 of the instant application only at a single residue, residue 70. The proteins are over 99.5% identical.

The courts have long recognized that sequencing errors can occur (*Ex parte Maizel*; 27

USPQ2d 1662, BPAI 1992, see especially pp. 1663 and 1666). The instant specification also recognizes that the sequences disclosed in their sequence listings and Figures may not be exact. Therefore, it is reasonable to expect that the single amino acid difference at position 70 of SEQ ID NO: 2 of the instant application and LaVallie et al. may be the result of a sequencing error, and that the actual clones of the instant application and LaVallie et al., in fact, have identical sequences.

The examiner is unable to determine whether the prior art disclosures actually possesses the characteristic of the sequence of SEQ ID NO: 2. Under such circumstances, where the product seems to be identical, then the burden shifts to applicant to provide evidence that the prior art would neither anticipate nor render obvious the claimed invention. Note the case law of *In re Best* 195 USPQ 430, 433 (CCPA 1977).

Claim 34 is rejected under 35 U.S.C. 103(a) as being unpatentable over LaVallie et al. as cited above in view of Hopp et al., U.S. Patent Number 5,011,912.

The teachings of LaVallie et al. are cited above. LaVallie et al. additionally teach pharmaceutical uses for the protein. LaVallie et al. does not teach expression of the protein as a fusion protein comprising an epitope tag or Fc region.

Hopp et al. teach the use of an amino acid sequence, "DYKDDDDK", which is disclosed as being immunogenic, for use in producing fusion proteins which can then be easily purified. See, for example, column 2, lines 45-57. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the protein of any one of the primary references by producing such as a fusion protein comprising the flag amino acid sequence of Hopp et al., for the purpose of being able to easily purify the proteins of the LaVallie patent. The motivation and expectation of success are both taught by Hopp et al. who teach the flag peptide/monoclonal antibody purification system as being generally useful for such.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

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U.S. Patent Number 5,679,783 (De Robertis et al.) disclose <sup>Frog</sup>~~mouse~~ chordin, see SEQ ID NO: 2. The cDNA encoding such is SEQ ID NO: 1. SEQ ID NO: 1 of De Robertis et al. is 84.7% identical to nucleotides 1047-1386 of SEQ ID NO: 6 of this application, with the longest contiguous region of identity being 33 residues.

YMS  
11/1/03

**Advisory Information:**

No claim is allowed.

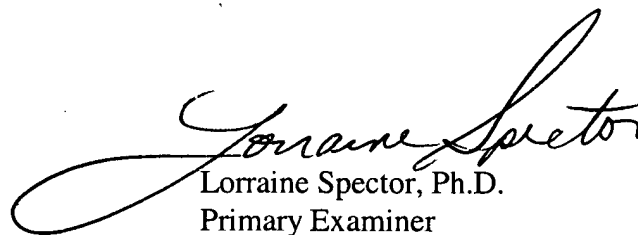
Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector, whose telephone number is (703) 308-1793. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 5:30 P.M.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary L. Kunz, at (703)308-4623.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to (703) 872-9306 (before final rejection) or (703)872-9307 (after final). Faxed draft or informal communications with the examiner should be directed to (703) 746-5228.

  
Lorraine Spector, Ph.D.  
Primary Examiner